More Biologic Therapies Expected To Treat Advanced Plaque Psoriasis

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Psoriasis is a T-cell–mediated autoimmune disorder that manifests as a variety of chronic inflammatory skin diseases requiring lifelong care.[1,2] Activated T cells release cytokines, which signal the accelerated turnover of epidermal cells, along with the keratinocyte and vascular changes that characterize the various forms of psoriasis.[3–5] Studies have isolated at least 36 genetic markers associated with these diseases.[6] The presence of T lymphocytes, cytokines, and dendritic cells in psoriatic lesions has led to the development of several biologic treatments.[7–9]

Psoriasis affects an estimated 7.4 million U.S. residents.[10] It can occur at any age but usually appears between the ages of 15 and 30 years.[11,12] The most common variant, plaque psoriasis (psoriasis vulgaris), affects an estimated 80% to 90% of people with psoriasis.[13–15] Of those with plaque psoriasis, approximately 20% have moderate-to-severe disease.[16] Plaque psoriasis is characterized by inflammatory, raised, dry plaques, which are usually covered by silvery-white scales. These lesions generally involve the scalp, face, trunk, and extensor surfaces of the forearms and shins (especially the elbows and knees).[17]

Other forms of psoriasis include flexural psoriasis (inverse or intertiginous psoriasis), which affects flexural body sites (skin folds) and genital areas; guttate psoriasis, which is characterized by small, drop-like lesions on the trunk, arms, and legs; generalized pustular psoriasis, which causes small pus-filled blisters; palmoplantar pustulosis, which affects the palms and the soles of the feet; and erythrodermic psoriasis, a potentially fatal disorder characterized by fiery redness and exfoliation of most of the body surface.[16–18]

Risk factors for psoriasis include psychological stress; the use of certain medications, including lithium, beta blockers, antimalarial drugs, and nonsteroidal anti-inflammatory drugs; oral steroid withdrawal; and streptococcal infection—all of which may stimulate T-cell proliferation.[19,20]

Individuals with any form of psoriasis are at increased risk of developing serious comorbid conditions, such as cardiovascular disease, diabetes mellitus, hypertension, inflammatory bowel disease, and lymphoma.[21–25] Psoriasis patients are also at risk of dyslipidemia, coronary calcification, increased C-reactive protein levels, decreased folate, and hyperhomocysteinemia.[26] Approximately one-third of psoriasis patients develop joint inflammation (psoriatic arthritis).[25,27]

Patients with mild plaque psoriasis are usually started on topical therapies, such as vitamin D products, topical corticosteroids, tar-based preparations, dithranol, salicylic acid, and vitamin A products.[28] These treatments are available as gels, foams, sprays, shampoos, lotions, ointments, soaps, and creams.[29] Topical treatment is often combined with phototherapy.[30,31] Patients with moderate-to-severe plaque psoriasis graduate to systemic therapy, with topical products relegated to occasional adjunctive use.[32] Commonly used systemic agents include methotrexate, cyclosporine, acitretin (Soriatane, Connetics Corporation), and apremilast (Otezla, Celgene).[32–34] Biologic therapies are the next step if systemic agents fail to produce an adequate response.[33] Established biologic treatments for adults with moderate-to-severe plaque psoriasis include adalimumab (Humira, AbbVie); etanercept (Enbrel, Amgen); infliximab (Remicade, Janssen); secukinumab (Cosentyx, Novartis); and ustekinumab (Stelara, Janssen) (Table 1).[34] Adalimumab and etanercept are the top U.S. therapies for advanced plaque psoriasis, followed by ustekinumab.[34]

Ixekizumab (Taltz, Eli Lilly), a humanized immunoglobulin G_4 monoclonal antibody (mAb),[34] received FDA approval in March 2016 as a new biologic treatment for moderate-to-severe plaque psoriasis.[35] Ixekizumab neutralizes the proinflammatory interleukin (IL)-17A cytokine.[34] By targeting IL-17A, it may also inhibit another proinflammatory cytokine, tumor necrosis factor alpha (TNFα).[35,36] Ana-

Table 1 Available Biologic Therapies for Patients With Moderate-to-Severe Plaque Psoriasis[35–37]

Drug Name *Company*	Therapeutic Class	FDA Approval
Adalimumab (Humira) *AbbVie*	IgG_1 mAb (TNFα inhibitor)	2008
Etanercept (Enbrel) *Amgen*	Dimeric fusion protein (TNFα and TNFβ inhibitor)	2004
Infliximab (Remicade) *Janssen*	$IgG_{1/K}$ mAb (TNFα inhibitor)	2006
Infliximab-dyyb (Inflectra) *Celltrion/Hospira*	Biosimilar to infliximab	2016
Ixekinumab (Taltz) *Eli Lilly*	IgG_4 mAb (IL-17A inhibitor)	2016
Secukinumab (Cosentyx) *Novartis*	$IgG_{1/K}$ mAb (IL-17A inhibitor)	2015
Ustekinumab (Stelara) *Janssen*	$IgG_{1/K}$ mAb (IL-12/23 p40 subunit inhibitor)	2009

IgG = immunoglobulin G; IL = interleukin; mAb = monoclonal antibody; TNF = tumor necrosis factor.

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Table 2 Pipeline Biologics for the Treatment of Adults With Moderate-to-Severe Plaque Psoriasis[34,38,41]

Product *Developers*	Therapeutic Class	Targeted Indication	Expected Dosing	Expected Pricing Strategy	FDA Status
Brodalumab *AstraZeneca/Valeant*	Anti–IL-17 receptor mAb	Adults with moderate-to-severe plaque psoriasis	140 mg or 210 mg SC every 2 or 4 weeks, depending on clinical response	Likely similar to secukinumab because both are IL-17 inhibitors with similar dosing schedules	BLA accepted in January 2016; PDUFA action date: November 16, 2016
Guselkumab (CNTO-1959) *Janssen*	Anti–IL-23 mAb	Adults with moderate-to-severe plaque psoriasis who are eligible for phototherapy or systemic therapy, or who have failed previous treatments	100 mg SC at weeks 0 and 4, and then every 8 weeks during maintenance regimen	Likely to be priced 10% to 15% higher than adalimumab because of slightly greater efficacy	In late-stage development; U.S. launch expected in 2017
Piclidenoson (CF-101) *Can-Fite Biopharma*	Adenosine A3 receptor agonist	Adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy	2 mg orally twice daily	40% discount to oral apremilast in order to be included in insurance formularies as first-line oral therapy	In late-stage development; U.S. launch expected in 2019
Tildrakizumab *Merck/Sun Pharmaceuticals*	Anti–IL-23 mAb	Adults with moderate-to-severe plaque psoriasis who are eligible for phototherapy or systemic therapy	100 mg or 200 mg SC every 12 weeks	Likely to be priced slightly lower than secukinumab because both are IL-23 inhibitors with similar dosing schedules and PASI scores	In late-stage development; U.S. launch expected in 2016
Tofacitnib (Xeljanz)* *Pfizer/Takeda*	JAK inhibitor	Adults with moderate-to-severe plaque psoriasis	10 mg orally twice daily (twice the RA dose)	Likely similar to etanercept because their efficacy profiles are similar	CRL in October 2015; FDA has requested additional safety data

* Tofacinitib is currently approved for the treatment of adults with moderate-to-severe RA who have had an inadequate response to or are intolerant of methotrexate.

BLA = biologics license application; CRL = complete response letter; IL = interleukin; JAK = Janus kinase; mAb = monoclonal antibody; PASI = Psoriasis Area and Severity Index; PDUFA = Prescription Drug User Fee Act; RA = rheumatoid arthritis; SC = subcutaneous.

lysts expect ixekizumab to be used as second- or third-line therapy after TNF failure, competing with secukinumab, another IL-17 inhibitor.[34]

The approval of ixekizumab was closely followed by regulatory clearance of infliximab-dyyb (Celltrion/Hospira) for the treatment of adults with chronic severe plaque psoriasis. Infliximab-dyyb is biosimilar to, but not interchangeable with, infliximab. It was the second biosimilar approved by the FDA.[37]

Five promising biologic agents are poised to enter the psoriasis market (Table 2). Brodalumab is under FDA review. Tofacitinib recently received a complete response letter from the agency but remains in active development. Guselkumab, piclidenoson, and tildrakizumab are undergoing phase 3 evaluations.

Brodalumab (AstraZeneca/Valeant), an mAb that acts as an IL-17 receptor antagonist, was developed specifically to treat adults with moderate-to-severe plaque psoriasis.[34] Unlike secukinumab and ixekizumab, brodalumab does not bind to the IL-17 cytokine itself.[34] Targeting the IL-17 receptor has been shown to reduce inflammation.[36] In May 2015, Amgen terminated its partnership with AstraZeneca as a co-developer of brodalumab because of the drug's increased risk of suicidal ideation and behavior.[38] In January 2016, the FDA accepted a biologics license application for brodalumab for the treatment of patients with moderate-to-severe plaque psoriasis and assigned a Prescription Drug User Fee Act (PDUFA) action date of November 16, 2016.[39] If approved, brodalumab is expected to become a third-line therapy for patients with moderate-to-severe plaque psoriasis after traditional biologic treatments fail.[34]

Guselkumab (CNTO-1959, Janssen) is an anti–IL-23 mAb with anti-inflammatory properties. It is being developed for the treatment of adults with moderate-to-severe plaque psoriasis and other forms of the disease, including pustular psoriasis, erythrodermic psoriasis, and psoriatic arthritis.[34] If guselkumab wins FDA approval, it is expected to grab a large share of the psoriasis market in 2017 as the first IL-23–specific inhibitor for advanced plaque psoriasis to win FDA approval.[34]

Piclidenoson (CF-101, Can-Fite Biopharma) is an orally bioavailable, selective A3 adenosine receptor agonist.[34] It down-regulates the nuclear factor-kappa/B signaling pathway, which in turn inhibits proinflammatory cytokines and chemokines, such as TNFα. In addition, piclidenoson affects certain cellular components of inflammation, such as autoreactive T cells.[40] Can-Fite is developing piclidenoson as a potential first-line oral treatment for adults with moderate-to-severe plaque psoriasis with an anticipated U.S. launch date of 2019.[34]

Tildrakizumab (Merck/Sun Pharmaceuticals) is an anti–IL-23 mAb that targets the IL-23 p19 subunit (IL-23 subunit alpha). The IL-23 protein is composed of p19 and p40 subunits; ustekinumab

targets p40.[34] Tildrakizumab is undergoing phase 3 evaluations as a treatment for adults with moderate-to-severe chronic plaque psoriasis; these trials are expected to continue until 2019. However, analysts anticipate tildrakizumab will launch in the U.S. in 2017.[34]

Tofacitninb (Xeljanz, Pfizer/Takeda) is an oral Janus kinase (JAK) inhibitor[41] that underwent FDA review last year as a potential treatment for adults with moderate-to-severe plaque psoriasis. In October 2015, the FDA issued a complete response letter asking for additional safety analyses, and Pfizer is working on that request.[42] Tofacitinib is approved in the U.S. for the treatment of patients with moderate-to-severe rheumatoid arthritis who have had an inadequate response to or are intolerant of methotrexate.[41] The drug is also in phase 3 development for the treatment of patients with ulcerative colitis, psoriatic arthritis, and idiopathic juvenile arthritis. Tofacitinib is the most-advanced JAK inhibitor targeting advanced plaque psoriasis, and analysts expect it will be a first-in-class product if it eventually wins FDA approval for that indication.[34]

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